A Three-Step Synthesis of Hydrogenated Tamoxifen

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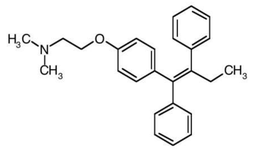
Abstract

Tamoxifen is an active molecule that is used to treat estrogen-receptor-positive breast cancer in both men and women. Estrogen-receptor-positive (ER+) breast cancer is where the cancer cells' growth is promoted by the presence of estrogen. Tamoxifen is an antagonist of the estrogen receptors in the breast tissue because it blocks the receptors, preventing cancer growth. Three steps were taken to synthesize hydrogenated tamoxifen. First, 1-phenyl-1-(p-hydroxyphenyl)-2-phenylbut-1-ene was synthesized from 4-hydroxybenzophenone and propiophenone, using THF as a solvent. Then, the product was amino alkylated to synthesize E and Z isomers of tamoxifen, to which it was hydrogenated to produce our final product, hydrogenated tamoxifen, or ethanamine. In order to make this process more green 2-methyltetrahydrofuran (2-meTHF) was used in place of THF wherever possible.

Introduction

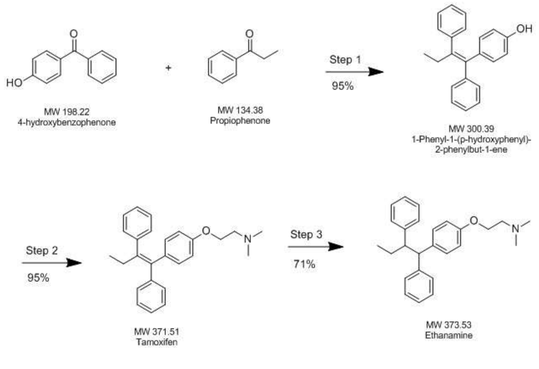


Tamoxifen is an active ingredient used to treat breast cancer. It is an anti-estrogen reagent because it blocks the growth of breast cancer by inhibiting estrogen receptors, and is mostly used in the earlier treatment of metastatic breast cancer in both men and women. 4-hydroxybenzophenone and propiophenone, using titanium chloride as a catalyst, were used as the main reactants for the first step of the synthesis of tamoxifen. These reagents were to undergo an Aldol condensation reaction to make the desired key intermediate. An Aldol condensation reaction requires an enol or an enolate ion to react with a carbonyl compound to form a β-hydroxyaldehyde or a β-hydroxyketone. Aldol reactions are a good way to form carbon-carbon bonds between two molecules and are widely used for pharmaceutical synthesis. Since no product was obtained from the Aldol Condensation reaction, a Wittig reaction was carried out using 4-hydroxybenzophenone, benzyltriphenylphosphonium chlorate, and potassium phosphate. A Wittig reaction consists of an aldehyde or a ketone reacted with a triphenylphosphonium ylide (called the Wittig reagent) to produce an alkene and a triphenylphosphine oxide. This is important in synthesizing organic molecules with fixed double bonds.

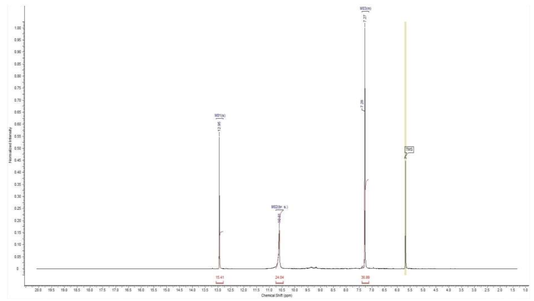
Incorporation of Green Chemistry

Green chemistry, which is a method that incorporates less hazardous reagents in order to eliminate waste and harm to the environment, was also incorporated into this experiment. Had the sought out product been obtained then the three-step synthesis would have been repeated using 2-methyltetrahydrofuran (2-meTHF) instead of tetrahydrofuran (THF). 2-meTHF reduces the amount of waste produced because of its low miscibility in water and also reduces reaction time because of its higher boiling point. During reflux, it also accounts for less solvent loss and saves energy during distillation.

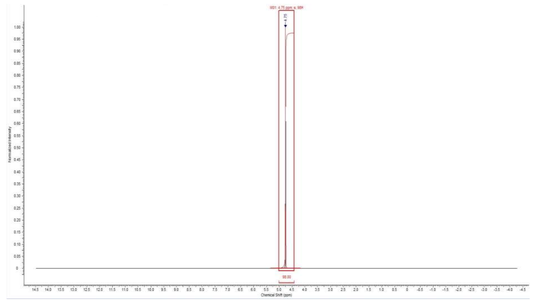
Synthetic Scheme



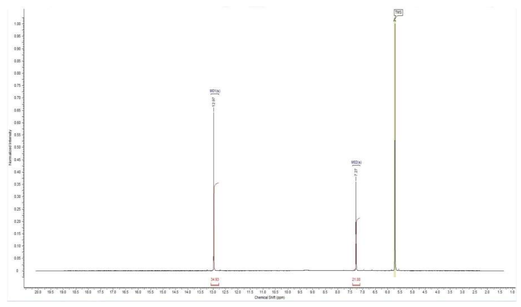
NMR, IR, and TLC data



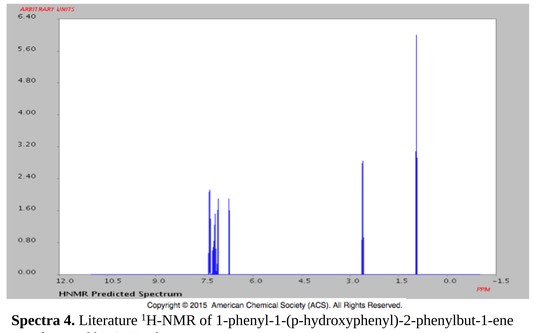
Spectra 1. ^{1}H-NMR of Aldol reaction with Chloroform-D.



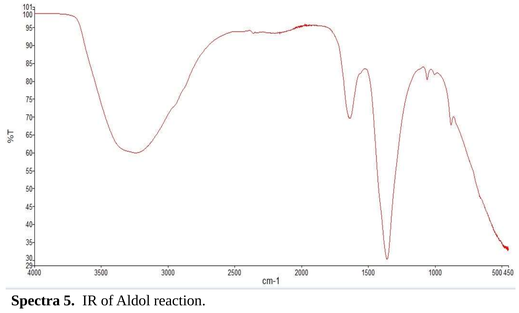
Spectra 2. ^{1}H-NMR of Aldol reaction with D_2O



Spectra 3. ^{1}H-NMR of Wittig reaction with Chloroform-D.



Spectra 4. Literature ^{1}H-NMR of 1-phenyl-1-(p-hydroxyphenyl)-2-phenylbut-1-ene as referenced by SciFinder.



Spectra 5. IR of Aldol reaction.

Figure 1. TLC plate developed in 50/50 toluene/chloroform (Aldol).

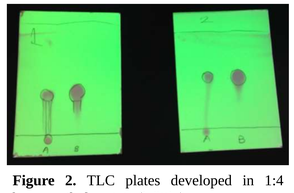


Figure 2. TLC plates developed in 1:4 hexane:ethyl acetate (Wittig).

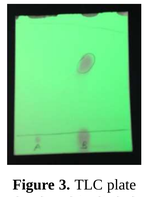


Figure 3. TLC plate developed in diethyl ether (Wittig).

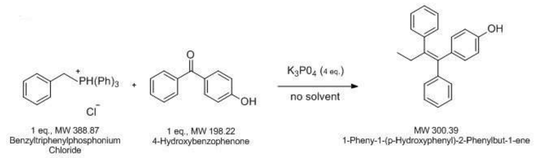
Figure 4. TLC plate developed in ethyl acetate (Wittig).

Green Chemistry Table

Comparison Parameter	THF	2-MeTHF
Hazards	Flammable, carcinogen, explosive, corrosive, lachrymator	Flammable, irritant
Cost	$54.60/100mL	$85.90/100mL
Percent yield	Not determined	Not determined
E factor	Not determined	Not determined
Reaction time, temperature	(Step 1) 1 day, 66° C	(Step 1) 4 hours, 80° C
Ease of separation	Hard	Easy
Product purity, byproducts	Not determined	Not determined
Waste produced	Not determined	Not determined

Discussion

The goal was to produce hydrogenated tamoxifen using first an Aldol condensation reaction, then an N-alkylation, and lastly an oxidation reaction of an alkene group. However, complications arose during the first step when the key intermediate was not obtained. This was determined by running NMR (Spectra 1 and 2) and IR (Spectra 5). NMR and IR did not show peaks expected for the key intermediate. TLC (Figure 1) produced an R_f value of 0 which did not match the literature R_f value of 0.35. A Wittig reaction was then used instead of an Aldol to produce the key intermediate (see reaction scheme below). The progress of the Wittig reaction was monitored by TLC (Figures 2 - 4), but no reaction was observed. This signified that the key intermediate was not obtained. After NMR spectroscopy, observed peaks (Spectra 3) did not correspond to the literature data of the desired product (Spectra 4). Potential sources of error include calculation errors in the amount of reagents used. When attempting the Wittig reaction, the reaction mixture was refluxed with several different solvents in an attempt to identify which one would dissolve it and allow development by TLC. This process could have exhausted the product. In the future more precise laboratory techniques and equipment can be incorporated to ensure success.



Conclusion

Using the Aldol condensation reaction and later on, the Wittig reaction, the first desired intermediate in the synthesis of 1-phenyl-1-(p-hydroxyphenyl)-2-phenylbut-1-ene was not obtained. These reactions were characterized by NMR, IR, and TLC and compared to literature values. Since no reaction occurred the yields for the individual steps and thus the overall yield was unable to be determined.

Future Directions

- Repeat the alternative step with the Wittig reaction using the solvent that dissolves the product.
- Look for other experimental methods to synthesize 1-phenyl-1-(p-hydroxyphenyl)-2-phenylbut-1-ene (e.g. Grignard).

References

- Greener Solvent Alternatives. Sigma Aldrich. 2010.
- McCaugee et al. Journal of Med. Chem. 30. 1987. 1761-1767.
- Rubin et al. Bioorg. Med. Chem. 9. 2001. 1579-1587.
- Shiina et al. Bioorg. Med. Chem. 15. 2007. 7599-7617.

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